NATURALISTA CAMPANO
ISSN: 1827-7160
Volume 28 Issue 1, 2024

Synthesis of 3,5,6-Substituted Uridine Derivatives as Potential Therapeutic Agents

C. Hazarathaiah Yadav[1*], Narendra Revanuri[2]

[1,2]Department of Chemistry, VelTech Rangarajan Dr Sagunthala R & D Institute of Science and Technology, Chennai, Tamil Nadu, India

Corresponding Email: info@anaxlab.com

Abstract: This study focuses on uridine derivatives with modifications at specific positions on the molecule, particularly at the 3rd, 5th, and 6th carbons. These modified uridines serve two main purposes of Intermediate Building Blocks and Potential Cancer Treatment They act as helpful intermediates, essentially building blocks, for the synthesis of even more complex uridine derivatives with additional substitutions.These substituted uridines themselves hold promise as therapeutic agents, particularly in tumor treatment. However, further research is needed to fully explore their effectiveness and potential applications.
Despite being discovered in 1959 and demonstrating impressive effectiveness against malignant tumors (U.S. Pat. No.2885398), 5-fluorouridine's high toxicity has limited its clinical application. 5-Trifluoromethyl-2'-deoxyuridine (5-CF3dUrd) demonstrates both anti-tumor activity (Cancer Research 24, 1979 [1964]) and antiviral properties (Cancer Research 30, 1549, 1970). These promising findings have fueled research into the potential therapeutic applications of 5-CF3dUrd and related derivatives.
This study details the synthesis of several substituted uridine derivatives using various approaches. The structures of these newly synthesized molecules were confirmed using ^{1}H-NMR and mass spectrometry. Our findings suggest that these derivatives possess potential as promising drug candidates for further evaluation in relevant therapeutic areas.

Keywords: Uridine derivatives, 3-substituted Uridine, 5-substituted Uridine, 6-substituted Uridine.

1. Introduction

In the foregoing situation, we conducted extensive research to prepare substituted uridine derivatives, which may be more useful for treating tumors uridine derivatives are useful as intermediates for preparing other substituted uridine derivatives also.
Many uridine derivatives with antimicrobial and anticancer activities fall into this category. An example is 5-Azacitidine, which is a drug used to treat certain types of leukemia.
Uridine derivatives are important for several reasons, Expanded Functionality: They offer a wider range of biological activities compared to uridine itself. By modifying the base or sugar structure, efforts are put to create derivatives with specific properties, such as targeting viruses, fighting cancer, or protecting nerve cells.
Uridine derivatives are a promising area of research for developing new therapeutic drugs. They can potentially address limitations of existing drugs, like improved targeting or reduced side effects. Studying how different uridine derivatives interact with cells can provide valuable insights into various biological pathways. This knowledge can then be used to develop new treatments or diagnostic tools.
Scaffolding for New Molecules: The basic structure of uridine derivatives can serve as a platform for designing entirely new molecules with unique functionalities. This opens doors for innovation in various fields, like drug discovery and materials science. Overall, uridine derivatives hold significant potential for advancing medicine, understanding biological processes, and creating novel molecules with diverse applications.
Therefore, synthesis of these derivatives mainly, 3-substituted Uridine, 5-substituted Uridine, 6-substituted Uridines are of our particular interest, and we are presenting few derivatives of interest.

2. Results and Discussion

This study successfully synthesized several noteworthy substituted uridine derivatives. To achieve these desired compounds, researchers employed a variety of reaction schemes. These schemes were strategically chosen to not only obtain the target molecules but also to ensure good yields. Furthermore, the reaction conditions used

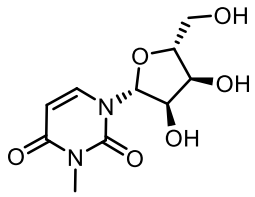
were considered mild, minimizing harsh chemicals or extreme temperatures. This approach is advantageous as it can potentially translate to a more cost-effective and scalable synthesis process in the future.

3-Substituted Uridine Derivatives

3-substituted uridine derivatives are a class of molecules derived from uridine, a nucleoside involved in RNA synthesis, with modifications at the 3rd carbon position of the ribose sugar ring. This specific modification can lead to interesting and potentially valuable properties.

The specific functional group attached at the 3rd carbon position can significantly influence the derivative's properties. This allows for targeted design of molecules with desired effects. While some 3-substituted uridine derivatives have shown promise, further research is needed to fully understand their mechanisms of action, optimize their potency and selectivity, and address potential safety concerns before widespread clinical use.

Overall, 3-substituted uridine derivatives represent a fascinating area of research with the potential to unlock novel therapeutic strategies. However, further exploration is crucial to fully realize their potential benefits.



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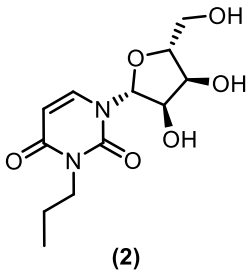

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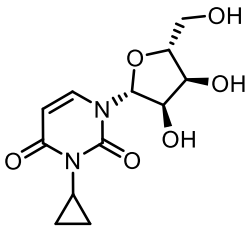

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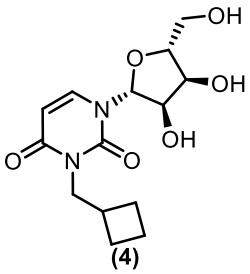

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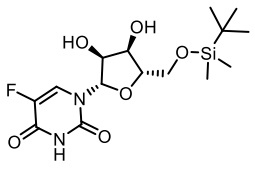
5-Substituted Uridine Derivatives

5-Substituted uridine derivatives are a diverse group of molecules derived from uridine, a nucleoside essential for RNA synthesis. These derivatives boast modifications at the 5th carbon of the ribose sugar ring, leading to a wide range of potential applications.

The beauty of 5-substituted uridine derivatives lies in their versatility. By incorporating different functional groups at the 5th position derivatives will have a variety of biological activities, such as Modulation of cellular processes, Anticancer properties, Antimicrobial effects.

Existing drugs like 5-Azacitidine, used for certain leukemias, demonstrate the promise of this class. However, further research is needed to Fully understand the mechanisms of action of different derivatives, optimize potency and selectivity to minimize side effects and to ensure safety and efficacy through rigorous clinical trials.

In conclusion, 5-substituted uridine derivatives hold immense potential for the development of novel therapeutic agents. Their versatility and tailorable properties offer exciting possibilities for treating various diseases. However, continued research is necessary to unlock their full potential and ensure their safe and effective use in medicine.



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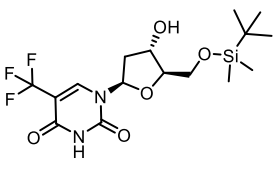

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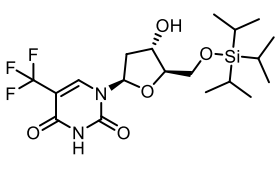

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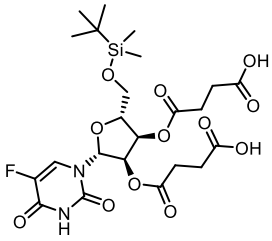

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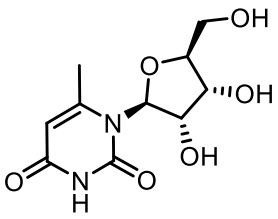
6-Substituted Uridine Derivatives

modifications on the 6th carbon of the uridine's uracil base. These modifications unlock a treasure trove of potential applications in medicinal chemistry. Unlike 5-substituted derivatives, modifications at the 6th position are less common in nature. This relative rarity translates into potentially unique properties and functionalities. Researchers are actively exploring these derivatives to discover novel biological activities. The type of functional group attached to the 6th carbon plays a crucial role in determining the derivative's properties. Strategically introduce various substituents like alkyl groups, halogens, or even complex aromatic moieties to achieve desired effects.

Strategic modifications can create derivatives that inhibit specific enzymes involved in disease processes, paving the way for targeted therapies. Despite the exciting potential, challenges remain in
Introducing modifications at the 6th position can be synthetically more challenging compared to 5th position modifications. The mechanisms of action for many 6-substituted derivatives are not fully understood, requiring further research for optimal development.
However, the potential rewards outweigh the challenges. With continued research efforts in synthesis, biological evaluation, and mechanism elucidation, 6-substituted uridine derivatives hold immense promise for the discovery of ground breaking therapeutic agents.



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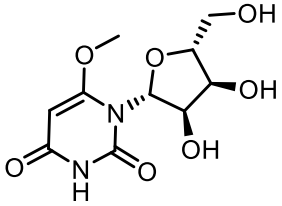

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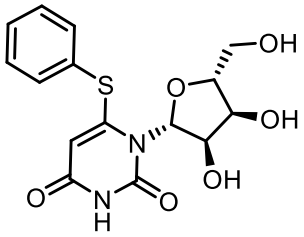

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3. Experimental Procedures:

Synthesis of 3-substituted uridine derivatives

3-methyluridine (1)

Uridine (0.735 g, 3.0 mmol) and potassium carbonate (0.705 g, 5.1 mmol) were dissolved in a mixture of DMF (5 mL) and acetone (5 mL).Methyliodide (0.187 mL, 4.5 mmol) was then slowly added dropwise to the solution.The reaction mixture was heated under reflux at 50-60 °C for 4 hours. After evaporation of the solvent, the residue was purified using silica gel column chromatography with a solvent system of chloroform/ethyl acetate/methanol (5:4:1 v/v/v). Crystallization from methanol, ethyl acetate, and petroleum ether afforded the desired product (973 mg, 62.8% yield).
1H NMR (D20) 3.16(3H,s,CH3), 3.66-3.80(2H,m,H-5',H-5''), 3.92-4.24 (3H,m,H-2',H-3',H-4') ,5.68-5.76 (2H,m,H-l',H-5), 7.54-7.62 (1H,d,J=8Hz,H-6).
MS(ESI) m/z calcd for C10H14N2O6, 258.23 [M+H+] found 259.33.

N^3-allyluridine (2a)

2a is prepared in similar was to that of compound (1) 3-methyluridine, using allyl bromide in place of Methyl iodide and recrystallized with ethyl acetate with the yield of 70%

3-propyluridine (2)

Compound was prepared from 2a. Compound 2a (284mg,1.0mmol) and 10% palladium on activated carbon 100mg were dissolved in 10mL of ethanol and hydrogenated with hydrogen gas. The mixture was filtered, and ethanol was removed in vacuo. The residue was crystallized from ethylacetate ,yielding 168mg(64%yield)
1H NMR (D20) 0.96(3H,t,CH3), I.52-1.82 (2H,m,CH2) ,3.84-4.16 (4H,m,H-5',H-5'',NCH2) , 4.18-4.62 (3H, m, H-2', H-3', H-4'), 6.14-6.30(2H, m, H-l', H-5), 8.26(1H, d, J=8Hz,H-6).
MS(ESI) m/z calcd for C12H18N2O6, 286.28 [M+H+] found 288.68.

3-Cyclopropaneuridine (3) and 3-Methylcyclo butane uridine (4):

Both compound 3 and 4 were also prepared in the same fashion to that of compound 1, whereas for 3 chlorocyclopropane and for 4 (chloromethyl) cyclobutene has been used. crystallized from ethyl acetate, yielding 60% of **3** and 54% of **4**.

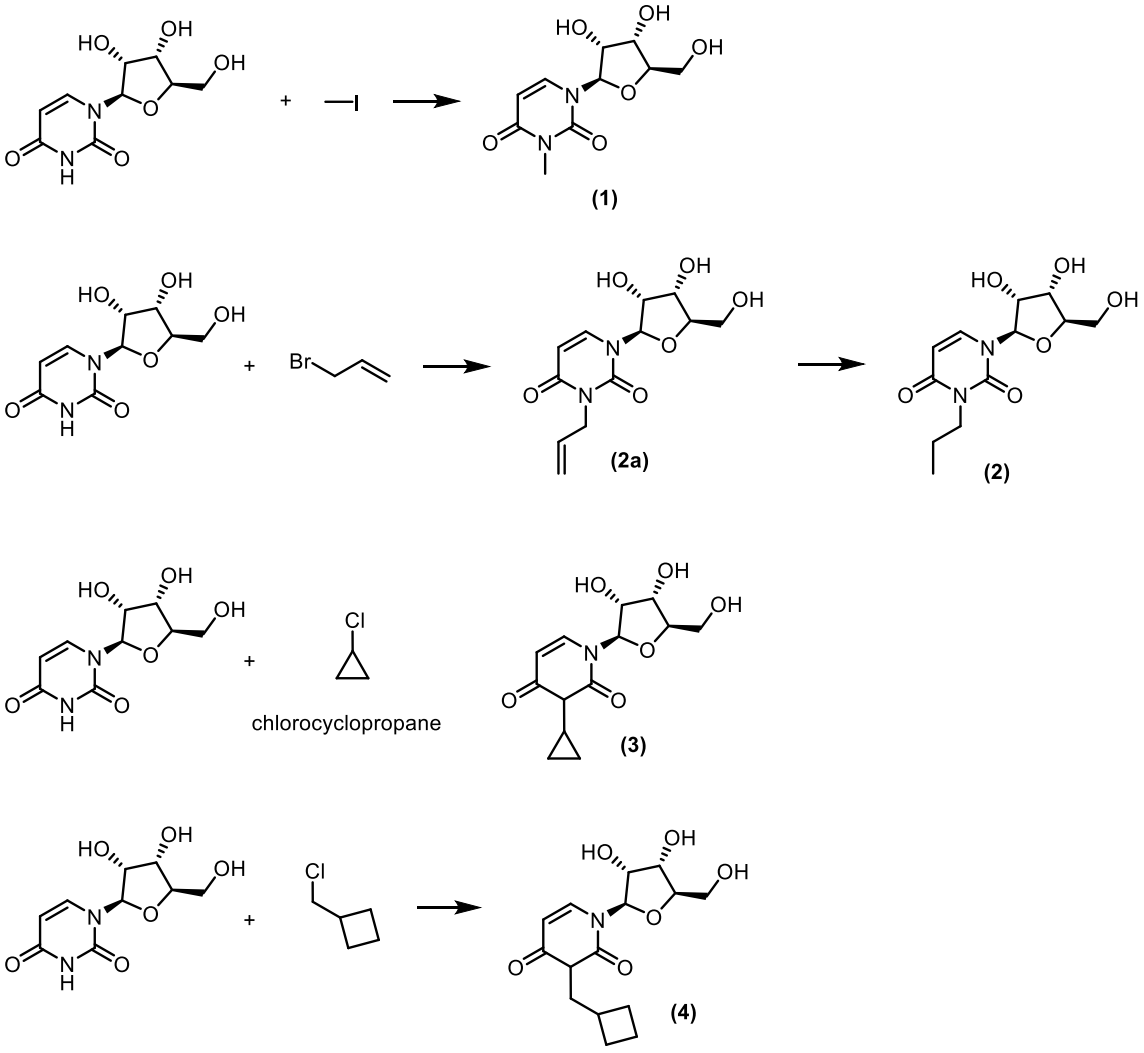
1H NMR (D20)1.70 (3H,s,CH3), 1.78 (3H,s,CH3), 3.80-3.92 (2H,m,H-5',H-5''), 3.96-4.38 (3H,m,H-2',H-3',H-4'), 4.48 (2H,d,J=8Hz,NCH2), 4.96-5.14 (1H,m,C=CH), 5.86-6.00 (2H,m,H-l',H-5), 7.88 (1H,d,J=8Hz,H-6).

MS(ESI) m/z calcd for C13H17NO6, 283.28 [M-H+] found 282.19.

1H NMR (D2O) 0.96 (3H,t,CH3), I.52-1.82 (2H,m,CH2), 3.84-4.16 (4H,m,H-5',H-5'',NCH2), 4.18-4.62 (3H,m,H-2',H-3',H-4'), 6.14-6.30 (2H,m,H-l',H-5), 8.26 (1H,d,J=8Hz,H-6).

MS(ESI) m/z calcd for C15H21NO6, 311.33 [M-H+] found 310.21

Synthetic scheme for preparation of 3-substituted uridine derivatives (1-4)



Synthesis of 5-Substituted Uridine Derivatives

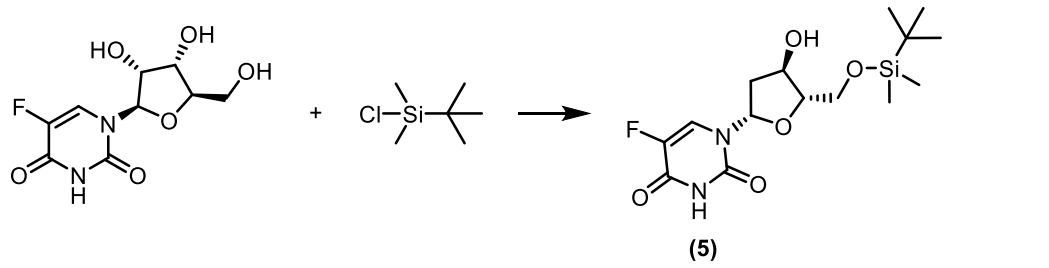
General procedure:

Representative for preparation of compound (5)
1-((2S,3S,4R,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)-5-fluoropyrimidine-2,4(1H,3H)-dione (5)
1.50 grams (3.81 mmol) of 5-fluorouridine was dissolved it in 5ml of N,N-dimethylformamide. Then, added 690mg (4.58 millimoles) of tert-butyldimethylsilyl chloride and 400mg of imidazole to the solution. The mixture reacted at room temperature for 10 hours.

Afterward, cooled the reaction mixture and added 50ml of water. Then extracted the mixture with ethyl acetate three times, using 50 ml each time. Combined the organic extracts, washed them with water and brine, and dried them using anhydrous magnesium sulfate.
Finally, removed the solvent using reduced pressure. This gave us a crude product that we further purified by column chromatography. We then recrystallized the product from ether, which yielded 1.1 grams of the desired white crystalline product. This represents a yield of 60%.

1H NMR (DMSO-d6) 0.08 (s, 6H, (CH3)2Si), 0.88 (s, 9H, (CH3)3), 2.05-2.11 (m, 1H, H-2, 3JH2H1 = 6.60 Hz, 3JH2H3 = 6.20 Hz, 2JH2H2 = 13.4 Hz), 2.13-2.18 (ddd, 1H, H-2 α, 3JH2 H1 = 5.00 Hz, 3JH2 H3 = 3.60 Hz, 2JH2H2 = 13.4 Hz), 3.73-3.76 (dd, 1H, H-5, 3JH5H4 = 3.00 Hz, 2JH5H5 = 10.5 Hz), 3.81-3.84 (m, 2H, H-5, H-4, 3JH5 H4 = 2.3 Hz, 2JH5H5 =10.5Hz), 4.19-4.21 (m, 1H, H-3, 3JH3H2 =6.20Hz, 3JH3H2 =3.60Hz, 3JH3H4 = 3.55 Hz), 5.32 (d, 1H, 3-OH, 3JHH = 4.65 Hz), 6.10-6.13 (m, 1H, H- 1, 3JH1H2 = 6.60 Hz, 3JH1H2 = 5.00 Hz), 7.97 (d, 1H, H-6, 3JHF = 6.9), 12.00 (brs, 1H, NH).
MS(ESI) m/z calcd for C15H25FN2O6Si , 376.46 [M-H+] found 377.57
Compound 6-8 were prepared in similar process as of compound 5.

Synthetic scheme for preparation of 5-substituted uridine derivatives (5-8)



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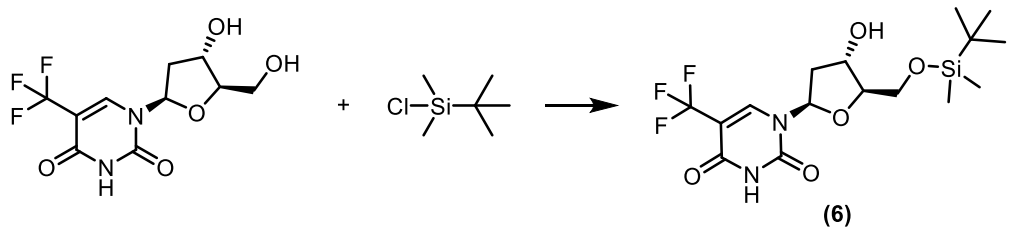

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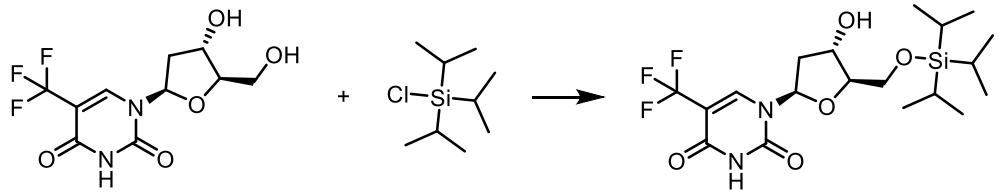

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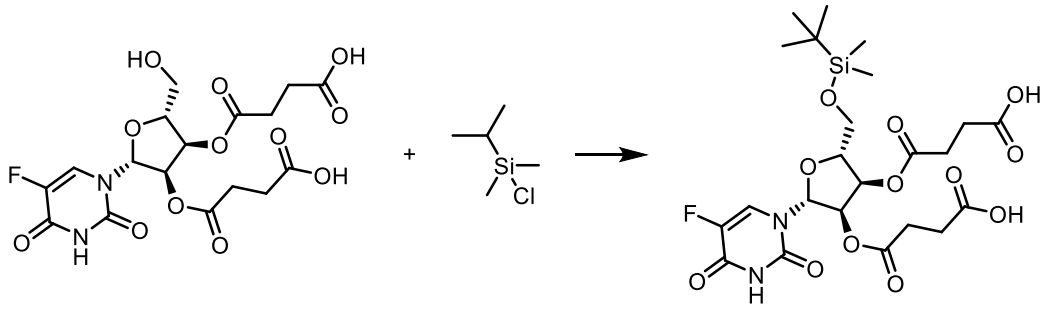

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Conflict of Interest Statement:

Authors declare no conflict of interest.

Acknowledgement

Authors acknowledge the great support extended by management of Veltech and Anax Laboratories for financial support and facility utilization permissions.

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